DOCKET NO: 239775US0DIV

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:
DAVID LEWIS ET AL.	: EXAMINER: HAGHIGHATIAN, M.
SERIAL NO: 10/612,072	:
FILED: JULY 3, 2003	: GROUP ART UNIT: 1616
FOR: PRESSURISED METERED DOSE INHALERS (MDI)	:

CORRECTED APPEAL BRIEF UNDER 37 C.F.R. § 41.37

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

This is an appeal of the Final Rejection dated February 15, 2007, of Claims 11-14, 16-19, 21-26, 28-32, 35-46, 48, and 49. A Notice of Appeal, along with a three-month extension of time and a Request for Reconsideration, was timely filed on August 15, 2007.

I. REAL PARTY IN INTEREST (37 C.F.R. § 41.37(c)(i))

The real party in interest in this appeal is Chiesi Farmaceutici S.p.A., having an place of business at Via Palermo, 26/A, Parma, Italy.

II. RELATED APPEALS AND INTERFERENCES (37 C.F.R. § 41.37(c)(ii))

Appellants, appellants' legal representative and the assignee are aware of no appeals, interferences, or judicial proceedings which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS (37 C.F.R. § 41.37(c)(iii))

Claims 11-14, 16-19, 21-26, 28-32, 35-46, 48, and 49 stand rejected.

Claims 1-10, 15, 20, 27, 33, 34, and 47 have been canceled.

No claims have been identified as having been allowed or confirmed.

No claims have been identified as being objected to.

Claims 11-14, 16-19, 21-26, 28-32, 35-46, 48, and 49 are being appealed.

IV. STATUS OF AMENDMENTS (37 C.F.R. § 41.37(c)(iv))

An amendment under 37 CFR 1.116 was filed on August 15, 2007. In the Advisory Action dated August, 24, 2007, the Examiner indicated that the Amendment filed on August 15, 2007, would be entered for the purposes of appeal.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER (37 C.F.R. § 41.37(c)(v))

Claim 11 is an independent claim and is drawn to:

an aerosol formulation comprising budesonide (*see*, page 8, lines 19-27, of the present specification), a propellant vehicle (*see*, page 7, lines 8-11, of the present specification), and an antioxidant (*see*, page 7, line 13, to page 8, line 6, of the present specification)

wherein said budesonide is completely dissolved in the propellant vehicle (*see*, page 10, lines 6-9, of the present specification) and said propellant consists of one or more

hydrofluroralkanes (*see*, page 7, lines 8-11, of the present specification) and a cosolvent (*see*, page 7, lines 12-13, of the present specification).

Claim 19 is an independent claim and is drawn to:

a pressurized metered dose inhaler (*see*, page 6, lines 13-18, of the present specification) comprising a container (*see*, page 6, lines 13-18, of the present specification) equipped with a metering valve (*see*, page 6, lines 13-18, of the present specification) and containing a pressurized aerosol formulation comprising

budesonide (*see*, page 8, lines 19-27, of the present specification), a propellant vehicle (*see*, page 7, lines 8-11, of the present specification), and an antioxidant (*see*, page 7, line 13, to page 8, line 6, of the present specification), wherein said budesonide is completely dissolved in the propellant vehicle (*see*, page 10, lines 6-9, of the present specification) and said propellant consists of one or more hydrofluroralkanes (*see*, page 7, lines 8-11, of the present specification) and a cosolvent (*see*, page 7, lines 12-13, of the present specification).

Claim 26 is an independent claim and is drawn to:

a method for the treatment of a bronchial disorder in a subject in need thereof (*see*, page 1, lines 9-11, of the present specification) comprising administering to said subject an aerosol formulation comprising

budesonide (*see*, page 8, lines 19-27, of the present specification), a propellant vehicle (*see*, page 7, lines 8-11, of the present specification), and an antioxidant (*see*, page 7, line 13, to page 8, line 6, of the present specification), wherein said budesonide is completely dissolved in the propellant vehicle (*see*, page 10, lines 6-9, of the present specification) and said propellant consists of one or more hydrofluroralkanes (*see*, page 7, lines 8-11, of the present specification) and a cosolvent (*see*, page 7, lines 12-13, of the present specification).

There are no other independent claims.

There are no means plus function or step plus function limitations in any of the independent claims involved in the appeal or any of the dependent claims which are argued separately under 37 C.F.R. § 41.37(c)(vii)).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

(37 C.F.R. § 41.37(c)(vi))

The rejection of Claims 11-14, 16-19, 21-26, 28-32, 39-46, 48, and 49 under 35 U.S.C. §103(a) in view of U.S. Patent No. 6,129,905 (Cutie) in view of U.S. Patent No. 5,776,433 (Tzou et al.) is to be reviewed.

The rejection of Claims 35-38 under 35 U.S.C. §103(a) in view of U.S. Patent No. 6,129,905 (Cutie) in view of U.S. Patent No. 5,776,433 (Tzou et al.) and further in view of U.S. Patent No. 6,558,651 (Riebe et al.) is to be reviewed.

The "provisional" rejection of Claims 11-14, 16-19, 21-26, 28-32, 35-46, 48, and 49 under the doctrine of obviousness-type double patenting in view of the claims of U.S. Patent Application Serial No. 10/244,519, now U.S. Patent No. 7,223,381 ("the '381 patent"), is to be reviewed.

VII. ARGUMENT (37 C.F.R. § 41.37(c)(vii))

A. The Rejection of Claims 11-14, 16-19, 21-26, 28-32, 39-46, 48, and 49 under 35 U.S.C. §103(a) in view of U.S. Patent No. 6,129,905 (Cutie) in view of U.S. Patent No. 5,776,433 (Tzou et al.)

Claims 11-14, 16-19, 21-26, 28-32, 39-46, 48, and 49 stand rejected under 35 U.S.C. §103(a) in view of U.S. Patent No. 6,129,905 (Cutie) in view of U.S. Patent No. 5,776,433 (Tzou et al.). That rejection is untenable and should be REVERSED.

Present Claims 11-14 and 16-18 relate to aerosol formulations which comprise budesonide, a propellant vehicle, and an antioxidant, wherein the budesonide is completely dissolved in the propellant vehicle and said propellant consists of one or more hydrofluroralkanes and a cosolvent.

Present Claims 19, 21-25, and 35-46 relate to pressurized metered dose inhalers which comprising a container equipped with a metering valve and which contain such an aerosol formulation. Present Claims 26, 28-32, 48, and 49 relate to methods for the treatment of a bronchial disorder in a subject in need thereof comprising administering to said subject such an aerosol formulation.

Thus, all of the present claims explicitly require the presence of a formulation which contains budesonide and that the budesonide be completely dissolved.

The cited references contain no disclosure or suggestion of the presently claimed aerosol formulations, pressurized metered dose inhalers, or methods. Accordingly, these references cannot affect the patentability of the present claims.

On page 6 of the Office Action, the position is taken that Cutie "teaches solutions of active agents such as budesonide, cosolvents such as ethanol, propellants such as HFA 134a and excipeints such as antioxidants." However, this assertion is simply incorrect.

It is true that in the section entitled "Background of the Invention," Cutie discloses a wide variety of aerosol formulations for oral inhalation, including dry-powder formulations, solutions, suspensions, and combination slurry-solutions (*see*, col. 1, line 24, to col. 3, line 12). However, Cutie does not disclose that any of the formulations discussed in the "Background of the Invention" section contain budesonide.

The only time Cutie mentions budesonide is in connection with formulations, which are clearly ***not*** solutions. Specifically, the only mention of budesonide in Cutie is in connection with the ***"inventive"*** formulations:

> Drugs which may be administered via the ***inventive formulations*** include: flunisolide, flunisolide hemihydrate, cromolyn sodium, isoproterenol sulfate, metaproterenol sulfate, ipratropium bromide, terbutaline sulfate, beclomethasone, beclomethasone dipropionate, beclomethasone monopropionate, albuterol, dexamethasone, dexamethasone sodium phosphate, isoproterenol HCl, phenylephrine bitartrate, epinephrine, epinephrine bitartrate, ergotamine tartrate, triamcinolone acetonide, ***budesonide***, fluticoside, salmeterol xinafoate, perbuterol sulfate, and pharmaceutically acceptable salts and derivatives of any of these drugs.

Cutie, col. 4, lines 24-36, emphasis added.

The fact that the inventive formulations of Cutie are dispersions, not solutions, is made abundantly clear in the very first sentence of the section entitled "Detailed Description of the Invention":

> The present invention provides an aerosol formulation for mucosal or topical administration comprising a therapeutically effective amount of at least one drug (active), a sugar and optionally one or more pharmaceutically acceptable excipients, ***dispersed*** in a pharmaceutically acceptable propellant or mixture of such propellants.

Cutie, col. 3, lines 46-51, emphasis added.

This understanding is reinforced by the disclosure of the role of the sugar:

> The sugar is capable of (1) facilitating the dispersion of the drug(s) and/or excipients; (2) stabilizing formulations, either physically, chemically, or both; (3) facilitating the transfer of aerosolized drug; (4) facilitating the drug's micronization and/or deaggregation or manipulating other in vitro qualities of the drug or formulation containing the same; (5) acting as a respiratory sensitizer or desensitizer of drug surface interactions at topical and/or mucosal surfaces; and (6) acting as a density modifier.

Cutie, col. 4, lines 16-24.

In addition, Cutie makes it clear that both the sugar and the active agent remain in solid form in the formulation right up to administration:

> The particle size of the sugar should be no greater than 10 microns diameter, since larger particles are not transported to the airways effectively. Preferably substantially all of the particles should be less than 5 microns in diameter. Most preferably substantially all of the particles should be less than about 2 microns in diameter. There is no lower limit on particle size except that which will be readily absorbed and retained on or in body tissues. When particles of less than about one-half micron in diameter are administered by inhalation, they tend to be exhaled by the patient.

Cutie, col. 4, line 62, col. 5, line 4.

> The particle size of the micronized drug should be no greater than 100 microns in diameter, since larger particles may clog the value or orifice of the container. Preferably, substantially all of the particles should be less than 25 microns in diameter. More preferably, substantially all of the particles should be less than about 10 microns in diameter. Most preferably, substantially all of the particles should be from about 0.5 to about 8 microns in diameter.

Cutie, col. 5, lines 11-17.

Thus, Cutie does not disclose any formulations in which budesonide is completely dissolved in the propellant. Instead, this reference only discloses dispersion formulations. Moreover, there is nothing in this reference which would motivate one of skill in the art to prepare a formulation in which budesonide is completely dissolved in the propellant or that it would even be possible to prepare such a formulation.

Applicants respectfully submit that there is nothing in Tzou et al. which can cure this basic deficiency of Cutie. Quite simply, Tzou et al. is completely silent in regard to budesonide. Instead, Tzou et al. only discloses aerosol compositions comprising flunisolide, ethanol and HFA propellants. Again, no reference is made in this reference of budesonide.

Thus, even the combined teachings of Cutie and Tzou et al. fail to disclose or suggest any aerosol formulation in which budesonide is dissolved in a propellant. In fact, from the teachings of Cutie and Tzou et al., one of skill in the art would have no motivation for even attempting to prepare an aerosol formulation in which budesonide is dissolved in a propellant or have any expectation of success that it would be possible to prepare such a formulation.

For this simple reason, even the combined teachings of Cutie and Tzou et al. cannot make a *prima facie* case of obviousness against the present claims.

Further, Cutie only mentions antioxidants in connection with dispersion formulations; there is no teaching in this reference which would suggest adding an antioxidant to a solution formulation. There is no mention at all of antioxidants in Tzou et al. Thus, even in

combination, these references fail to suggest the addition of an antioxidant to a solution formulation.

For all the above-given reasons, it is respectfully requested that the rejection be REVERSED.

B. The Rejection of Claims 35-38 under 35 U.S.C. §103(a) in view of U.S. Patent No. 6,129,905 (Cutie) in view of U.S. Patent No. 5,776,433 (Tzou et al.) and further in view of U.S. Patent No. 6,558,651 (Riebe et al.)

Claims 35-38 stand rejected under 35 U.S.C. §103(a) in view of U.S. Patent No. 6,129,905 (Cutie) in view of U.S. Patent No. 5,776,433 (Tzou et al.) and further in view of U.S. Patent No. 6,558,651 (Riebe et al.). That rejection is untenable and should be REVERSED.

As explained above, even the combined teachings of Cutie and Tzou et al. fail to suggest any aerosol formulation in which budesonide is dissolved in a propellant or any solution formulation which contains an antioxidant. The argument in section VII A in regard to the rejection of Claims 11-14, 16-19, 21-26, 28-32, 39-46, 48, and 49 under 35 U.S.C. §103(a) in view of Cutie in view of Tzou et al. is expressly incorporated by reference in this section. There is nothing in Riebe et al. which can make up these shortcomings.

Riebe et al. discloses the use of a recrystallised form of salbutamol sulphate to reduce or eliminate the problem of drug *adhesion or deposition* to the inner surfaces of the MDI. Thus, Riebe et al. is directed toward powder formulations, not a formulation in which the active agent is dissolved in the propellant.

For this simple reason, even the combined teachings of Cutie, Tzou et al., and Riebe et al. cannot make a *prima facie* case of obviousness against the present claims.

Moreover, it is important to note that Riebe et al. deals only with the specific problem of the adhesion of ***particulate*** salbutamol to the walls of the can. There would be no reason for the skilled in the art to turn to Riebe et al. to solve the problem of the addressed by the present claims, *i.e.*, chemical degradation of budesonide which is in ***solution***. Simply put, the problem of ***adhesion of a particulate*** drug does not exist in the case of the presently claimed metered dose inhalers, because the budesonide is dissolved and does not exist as a particulate drug.

Further, there is no suggestion in Riebe et al. that a solution to the specific problem of the adhesion of ***particulate*** salbutamol to the walls of a can would be at all relevant or applicable to a solution formulation.

Moreover, like Tzou et al., Riebe et al. is completely silent in regard to antioxidants, and Cutie only mentions antioxidants in connection with dispersion formulations. Thus, there is no teaching in any of these references, even taken in combination, which would suggest adding an antioxidant to a solution formulation.

For all the above-given reasons, it is respectfully requested that the rejection be REVERSED.

C. The Provisional Rejection of Claims 11-14, 16-19, 21-26, 28-32, 35-46, 48, and 49 under the Doctrine of Obviousness-Type Double Patenting in view of the Claims of U.S. Patent Application Serial No. 10/244,519, now U.S. Patent No. 7,223,381 ("the '381 patent")

Claims 11-14, 16-19, 21-26, 28-32, 35-46, 48, and 49 stand provisionally rejected for obviousness-type double patenting in view of the claims of U.S. Patent Application Serial No. 10/244,519, now U.S. Patent No. 7,223,381 ("the '381 patent"). That rejection is untenable and should be REVERSED.

As noted above, all of the pending claims require the presence of an antioxidant. Quite simply, there is nothing in any of the claims of the '381 patent which would suggest an aerosol formulation which contains an antioxidant. For the Board's convenience a copy of the '381 patent is attached hereto in Evidence Appendix. In addition, the claims of the '381 patent are repeated below:

1. A pressurized metered dose inhaler comprising a container equipped with a metering valve and containing a pressurized solution aerosol formulation comprising: Budesonide; a hydrofluorocarbon propellant; and a cosolvent present in an amount that dissolves or solubilizes said Budesonide in the mixture of cosolvent and propellant.

2. The pressurized metered dose inhaler of claim 1, wherein said cosolvent is ethanol.

3. The pressurized metered dose inhaler of claim 1, wherein said ethanol is present in an amount of 13% by weight.

4. The pressurized metered dose inhaler of claim 1, wherein said hydrofluorocarbon propellant is selected from the group consisting of HFA 227 and HFA 134a.

5. A pressurized metered dose inhaler comprising a container equipped with a metering valve and containing a pressurized solution aerosol formulation comprising: about 0.08% by weight of Budesonide; about 85.6% by weight of a

hydrofluorocarbon propellant; and a cosolvent present in an amount that dissolves or solubilizes said Budesonide in the mixture of cosolvent and propellant.

6. The pressurized metered dose inhaler of claim 5, wherein said cosolvent is ethanol.

7. The pressurized metered dose inhaler of claim 5, wherein said ethanol is present in an amount of 13% by weight.

8. The pressurized metered dose inhaler of claim 5, wherein said hydrofluorocarbon propellant is selected from the group consisting of HFA 227 and HFA 134a.

9. A pressurized metered dose inhaler comprising a container equipped with a metering valve and containing a pressurized solution aerosol formulation comprising: about 0.08% by weight of Budesonide; about 85.6% by weight of HFA 134a as a propellant; and about 13% by weight of ethanol, wherein said ethanol is present in an amount that dissolves or solubilizes said Budesonide in the mixture of cosolvent and propellant.

10. A pressurized metered dose inhaler comprising a container equipped with a metering valve and containing a pressurized solution aerosol formulation comprising: about 0.08% by weight of Budesonide; about 85.6% by weight of HFA 227 as a propellant; and about 13% by weight of ethanol, wherein said ethanol is

present in an amount that dissolves or solubilizes said Budesonide in the mixture of cosolvent and propellant.

11. A solution aerosol formulation adapted for use in a pressurized aerosol container, said aerosol formulation being formulated from a composition comprising: Budesonide; a hydrofluorocarbon propellant; and a cosolvent present in an amount that dissolves or solubilizes said Budesonide in the mixture of cosolvent and propellant.

12. The solution aerosol formulation of claim 11, wherein said cosolvent is ethanol.

13. The solution aerosol formulation of claim 11, wherein said ethanol is present in an amount of 13% by weight.

14. The solution aerosol formulation of claim 11, wherein said hydrofluorocarbon propellant is selected from the group consisting of HFA 227 and HFA 134a.

15. A solution aerosol formulation adapted for use in a pressurized aerosol container, said aerosol formulation being formulated from a composition comprising: about 0.08% by weight of Budesonide; about 85.6% by weight of a hydrofluorocarbon propellant; and a cosolvent present in an amount that dissolves or solubilizes said Budesonide in the mixture of cosolvent and propellant.

16. The solution aerosol formulation of claim 15, wherein said cosolvent is ethanol.

17. The solution aerosol formulation of claim 15, wherein said ethanol is present in an amount of 13% by weight.

18. The solution aerosol formulation of claim 15, wherein said hydrofluorocarbon propellant is selected from the group consisting of HFA 227 and HFA 134a.

19. A solution aerosol formulation adapted for use in a pressurized aerosol container, said aerosol formulation being formulated from a composition comprising: about 0.08% by weight of Budesonide; about 85.6% by weight of HFA 134a as a propellant; and about 13% by weight of ethanol, wherein said ethanol is present in an amount that dissolves or solubilizes said Budesonide in the mixture of cosolvent and propellant.

20. A solution aerosol formulation adapted for use in a pressurized aerosol container, said aerosol formulation being formulated from a composition comprising: about 0.08% by weight of Budesonide; about 85.6% by weight of HFA 227 as a propellant; and about 13% by weight of ethanol, wherein said ethanol is present in an amount that dissolves or solubilizes said Budesonide in the mixture of cosolvent and propellant.

21. A pressurized metered dose inhaler comprising a container equipped with a metering valve and containing a pressurized solution aerosol formulation comprising: about 0.08% by weight of Budesonide; about 83.6% by weight of a hydrofluorocarbon propellant; and a cosolvent present in an amount that dissolves or solubilizes said Budesonide in the mixture of cosolvent and propellant.

22. The pressurized metered dose inhaler of claim 21, wherein said cosolvent is ethanol.

23. The pressurized metered dose inhaler of claim 21, wherein said ethanol is present in an amount of 15% by weight.

24. The pressurized metered dose inhaler of claim 21, wherein said hydrofluorocarbon propellant is selected from the group consisting of HFA 227 and HFA 134a.

25. A solution aerosol formulation adapted for use in a pressurized aerosol container, said aerosol formulation being formulated from a composition comprising: about 0.08% by weight of Budesonide; about 83.6% by weight of a hydrofluorocarbon propellant; and a cosolvent present in an amount that dissolves or solubilizes said Budesonide in the mixture of cosolvent and propellant.

26. The solution aerosol formulation of claim 25, wherein said cosolvent is ethanol.

27. The solution aerosol formulation of claim 25, wherein said ethanol is present in an amount of 15% by weight.

28. The solution aerosol formulation of claim 25, wherein said hydrofluorocarbon propellant is selected from the group consisting of HFA 227 and HFA 134a.

As can be seen, there is no mention of antioxidant in any of these claims. In contrast, all of present Claims 1-14, 16-19, 21-26, 28-32, 35-46, 48, and 49 require the presence of an antioxidant.

Since the claims of the '381 patent do not recite an antioxidant, these claims cannot suggest any formulations which contain an antioxidant. Accordingly, the claims of the '381 patent cannot make present Claims 1-14, 16-19, 21-26, 28-32, 35-46, 48, and 49 obvious.

For all the above reasons, it is respectfully requested that the rejection be REVERSED.

CONCLUSION

For the above reasons, it is respectfully requested that all the rejections still pending in the Final Office Action be REVERSED.

Respectfully submitted,

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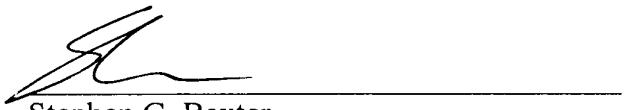

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CLAIMS APPENDIX (37 C.F.R. § 41.37(c)(viii))

A copy of Claims 11-14, 16-19, 21-26, 28-32, 35-46, 48, and 49 involved in the appeal appears below.

Claim 11. An aerosol formulation comprising budesonide, a propellant vehicle, and an antioxidant,

wherein said budesonide is completely dissolved in the propellant vehicle and said propellant consists of one or more hydrofluroralkanes and a cosolvent.

Claim 12. The formulation of claim 11, wherein said antioxidant is ascorbyl palmitate.

Claim 13. The formulation of claim 11, wherein said antioxidant is a tocopherol ester.

Claim 14. The formulation of claim 11, wherein said antioxidant is selected from the group consisting of ascorbic acid, ascorbyl palmitate, butylated hydroxytoluene, butylated hydroxyanisole, and tocopherol esters.

Claim 16. The formulation of claim 11, wherein the propellant vehicle is 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, or a mixture thereof.

Claim 17. The formulation of claim 11, wherein said cosolvent is an alcohol.

Claim 18. The formulation of claim 17, wherein said alcohol is ethanol.

Claim 19. A pressurized metered dose inhaler comprising a container equipped with a metering valve and containing a pressurized aerosol formulation comprising

budesonide, a propellant vehicle, and an antioxidant, wherein said budesonide is completely dissolved in the propellant vehicle and said propellant consists of one or more hydrofluroralkanes and a cosolvent.

Claim 21. The pressurized metered dose inhaler according to claim 19, wherein said propellant vehicle is 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, or a mixture thereof.

Claim 22. The pressurized metered dose inhaler according to claim 19, wherein said cosolvent is an alcohol.

Claim 23. The pressurized metered dose inhaler according to claim 22, wherein said alcohol is ethanol.

Claim 24. The pressurized metered dose inhaler according to claim 19, wherein said antioxidant is ascorbyl palmitate.

Claim 25. The pressurized metered dose inhaler according to claim 19, wherein said antioxidant is a tocopherol ester.

Claim 26. A method for the treatment of a bronchial disorder in a subject in need thereof comprising administering to said subject an aerosol formulation comprising

budesonide, a propellant vehicle, and an antioxidant, wherein said budesonide is completely dissolved in the propellant vehicle and said propellant consists of one or more hydrofluroralkanes and a cosolvent.

Claim 28. The method according to claim 26, wherein said propellant vehicle is 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane or a mixture thereof.

Claim 29. The method according to claim 26, wherein said cosolvent is an alcohol.

Claim 30. The method according to claim 29, wherein said alcohol is ethanol.

Claim 31. The method according to claim 26, wherein said antioxidant is ascorbyl palmitate.

Claim 32 . The method according to claim 26, wherein said antioxidant is a tocopherol ester.

Claim 35. The pressurized metered dose inhaler according to claim 19, wherein at least a part of the inner surfaces of said pressurized metered dose inhaler is composed of stainless steel.

Claim 36. The pressurized metered dose inhaler according to claim 35, wherein the entirety of the inner surfaces of said pressurized metered dose inhaler is composed of stainless steel.

Claim 37. The pressurized metered dose inhaler according to claim 19, wherein at least a part of the inner surfaces of said pressurized metered dose inhaler is composed of anodized aluminum.

Claim 38. The pressurized metered dose inhaler according to claim 37, wherein the entirety of the inner surfaces of said pressurized metered dose inhaler is composed of anodized aluminum.

Claim 39. The pressurized metered dose inhaler according to claim 19, wherein at least a part of the inner surfaces of said pressurized metered dose inhaler is coated with an inert organic coating.

Claim 40. The pressurized metered dose inhaler according to claim 39, wherein the inert organic coating is an epoxy-phenol resin coating.

Claim 41. The pressurized metered dose inhaler according to claim 39, wherein the inert organic coating is a multifunctional resin coating composed of an epoxy-phenol-novolac resin or an epoxy-cresol-novolac resin.

Claim 42. The pressurized metered dose inhaler according to claim 39, wherein the inert organic coating is a perfluoroalkoxyalcane resin or a fluorinated-ethylene-propylene polyether sulfone resin.

Claim 43. The pressurized metered dose inhaler according to claim 39, wherein the entirety of the inner surfaces of said pressurized metered dose inhaler is coated with an inert organic coating.

Claim 44. The pressurized metered dose inhaler according to claim 43, wherein the inert organic coating is an epoxy-phenol resin coating.

Claim 45. The pressurized metered dose inhaler according to claim 43, wherein the inert organic coating is a multifunctional resin coating composed of a epoxy-phenol-novolac resin or a epoxy-cresol-novolac resin.

Claim 46. The pressurized metered dose inhaler according to claim 43, wherein the inert organic coating is a perfluoroalkoxyalcane resin or a fluorinated-ethylene-propylene polyether sulfone resin.

Claim 48. The method according to claim 26, wherein said administering is metered dose administration to the respiratory tract of said subject via oral inhalation.

Claim 49. The method according to claim 26, wherein said aerosol formulation is contained within a pressurized metered dose inhaler comprising a container equipped with a metering valve.

EVIDENCE APPENDIX (37 C.F.R. § 41.37(c)(ix))

A copy of the claims as issued in U.S. Patent Application Serial No. 10/244,519, as shown in U.S. Patent No. 7,223,381 ("the '381 patent"), is attached hereto.

RELATED PROCEEDINGS APPENDIX (37 C.F.R. § 41.37(c)(x))

None.

US007223381B2

(12) **United States Patent**
Lewis et al.

(10) **Patent No.: US 7,223,381 B2**
(45) **Date of Patent: May 29, 2007**

(54) **PRESSURISED METERED DOSE INHALERS (MDI)**

(75) Inventors: **David Lewis**, Parma (IT); **David Ganderton**, Parma (IT); **Brian Meakin**, Bath (GB); **Paolo Ventura**, Parma (IT); **Gaetano Brambilla**, Parma (IT); **Raffaella Garzia**, Parma (IT)

(73) Assignee: **Chiesi Farmaceutici S.p.A.**, Parma (IT)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 184 days.

(21) Appl. No.: **10/244,519**

(22) Filed: **Sep. 17, 2002**

(65) **Prior Publication Data**

US 2003/0066525 A1 Apr. 10, 2003

Related U.S. Application Data

(62) Division of application No. 09/831,888, filed as application No. PCT/EP99/09002 on Nov. 23, 1999.

(30) **Foreign Application Priority Data**

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Jul. 30, 1999 (IT) MI99A001712

(51) **Int. Cl.**
A61K 9/12 (2006.01)
A61K 9/14 (2006.01)

(52) **U.S. Cl.** **424/45**; 424/489; 424/450; 514/630; 128/200.14

(58) **Field of Classification Search** 424/45, 424/46, 489, 450; 514/630; 128/200.14
See application file for complete search history.

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(57) **ABSTRACT**

The invention relates to the use of pressurized metered dose inhalers (MDIs) having part or all of their internal surfaces consisting of stainless steel, anodized aluminum or lined with an inert organic coating; and to compositions to be delivered with said MDIs.

28 Claims, No Drawings

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PRESSURISED METERED DOSE INHALERS (MDI)

This application is a continuation of U.S. application Ser. No. 09/831,888, filed on Jul. 19, 2001, which is a 371 of PCT/EP99/09002, filed Nov. 23, 1999.

The invention relates to the use of pressurised metered dose inhalers (MDIs) having part or all of their internal surfaces consisting of stainless steel, anodised aluminium or lined with an inert organic coating. The invention also relates to compositions to be delivered with said MDIs.

Pressurised metered dose inhalers are well known devices for administering pharmaceutical products to the respiratory tract by inhalation.

Active materials commonly delivered by inhalation include bronchodilators such as β2 agonists and anticholinergics, corticosteroids, anti-leukotrienes, anti-allergics and other materials that may be efficiently administered by inhalation, thus increasing the therapeutic index and reducing side effects of the active material.

MDI uses a propellant to expel droplets containing the pharmaceutical product to the respiratory tract as an aerosol.

For many years the preferred propellants used in aerosols for pharmaceutical use have been a group of chlorofluorocarbons which are commonly called Freons or CFCs, such as CCl_3F (Freon 11 or CFC-11), CCl_2F_2 (Freon 12 or CFC-12), and $CClF_2$-$CClF_2$ (Freon 114 or CFC-114).

Recently, the chlorofluorocarbon (CFC) propellants such as Freon 11 and Freon 12 have been implicated in the destruction of the ozone layer and their production is being phased out.

Hydrofluoroalkanes [(HFAs) known also as hydrofluorocarbons (HFCs)] contain no chlorine and are considered less destructive to ozone and these are proposed as substitutes for CFCs.

HFAs and in particular 1,1,1,2-tetrafluoroethane (HFA 134a) and 1,1,1,2,3,3,3-heptafluoropropane (HFA 227) have been acknowledged to be the best candidates for non-CFC propellants and a number of medicinal aerosol formulations using such HFA propellant systems have been disclosed.

Many of these applications, in which HFAs are used as propellant, propose the addition of one or more of adjuvants including compounds acting as co-solvents, surface active agents including fluorinated and non-fluorinated surfactants, dispersing agents including alkylpolyethoxylates and stabilizers.

In the international application n°PCT/EP98/03533 filed on Oct. 6, 1998 the applicant described solution compositions for use in an aerosol inhaler, comprising an active material, a propellant containing a hydrofluoroalkane (HFA), a cosolvent and further comprising a low volatility component to increase the mass median aerodynamic diameter (MMAD) of the aerosol particles on actuation of the inhaler.

Compositions for aerosol administration via MDIs can be solutions or suspensions. Solution compositions offer several advantages: they are convenient to manufacture being completely dissolved in the propellant vehicle and obviate physical stability problems associated with suspension compositions.

The widespread use of these formulations is limited by their chemical instability, causing the formation of degradation products.

WO94/13262 proposes the use of acids as stabilisers preventing the chemical degradation of the active ingredient in aerosol solution formulations comprising HFAs. Among the selected medicaments ipratropium bromide is comprised, for which many composition examples are supplied, in which the active ingredient is in combination with an organic or inorganic acid.

WO96/32099, WO96/32150, WO96/32151 and WO96/32345 disclose metered dose inhalers for the administration of different active ingredients in suspension in the propellant, wherein the internal surfaces of the inhaler are partially or completely coated with one or more fluorocarbon polymers optionally in combination with one or more non-fluorocarbon polymers.

Said applications do not however address the technical problem of the chemical stability of the active ingredient but they rather concern a different problem, namely that of the adhesion of micronized particles of the suspended active ingredient to the internal surfaces of the inhaler, such as the can walls, valves and sealings. It is also known from Eur. J. Pharm. Biopharm. 1997, 44, 195 that suspensions of drugs in HFA propellant are frequently subjected to absorption of the drug particles on the valves and on the internal walls of the inhaler. The properties of an epoxy phenol resin coating of the aerosol cans have been studied to circumvent this problem.

WO 95/17195 describes aerosol compositions comprising flunisolide, ethanol and HFA propellants. It is stated in the document that conventional aerosol canisters can be used to contain the composition and that certain containers enhance its chemical and physical stability. It is suggested that the composition can be preferably contained in vials coated with resins such as epoxy resins (e.g. epoxy-phenolic resins and epoxy-urea-formaldehyde resins).

Actually the results reported in Tables 5, 6 and 8 respectively on pages 16 and 19 of the cited application demonstrate that flunisolide decomposes only in plastic cans (Table 8), and that the percent drug recovery in compositions stored in aluminium, glass or epoxy-phenol formaldehyde resin coated vials is practically the same (Table 8). In other words there is no difference between aluminium, glass type III or epoxy/phenol-formaldehyde resin coated aluminium vials coated by Cebal. No data are reported for other types of epoxy resins.

It has now been found that the chemical stability problems of active ingredients in solution in HFA propellants can be eliminated by storing and delivering said composition employing metered-dose inhalers having part or all of their internal metallic surfaces consisting of stainless steel, anodised aluminium or lined with an inert organic coating.

The preferred material for the aerosol cans is anodised aluminium.

In the case of epoxy-phenol resin coating the choice of the suitable coating will be opportunely made on the basis of the characteristics of the active ingredient.

The most widely used epoxy resins in can coatings are produced by the reaction of epichlorohydrin and bisphenol A (DGEBPA). Variations in the molecular weight and in the polymerisation degree result in resins of different properties.

Phenoxy resins are other commercially important thermoplastic polymers derived from bisphenols and epichlorohydrin, characterized in that their molecular weights (MWs) are higher, ie, ca 45000, than those of conventional epoxy resins, ie, 8000 and lack terminal epoxide functionality.

Other multifunctional resins are epoxy-phenol-novolac and epoxy-cresol-novolac resins obtained by glycidylation of the phenol-formaldehyde (novolac) or of the o-cresol-formaldehyde (o-cresol novolac) condensates respectively.

The inhalers according to the invention effectively prevent the chemical degradation of the active ingredient.

Surprisingly and contrary to what reported in the prior art with regard to flunisolide, we found a considerable degradation of the tested active ingredients when their formulations were stored in glass containers type III.

SUMMARY OF THE INVENTION

Pressurised metered dose inhalers for dispensing solution of an active ingredient in a hydrofluorocarbon propellant, a co-solvent and optionally a low-volatility component characterized in that part or all of the internal surfaces of said inhalers consist of stainless steel, anodised aluminium or are lined with an inert organic coating.

DETAILED DESCRIPTION OF THE INVENTION

Pressurised metered dose inhalers are known devices, usually consisting of a main body or can, acting as a reservoir for the aerosol formulation, a cap sealing the main body and a metering valve fitted in the cap.

MDIs are usually made of a conventional material such as aluminium, tin plate, glass, plastic and the like.

According to the invention, part or all of the internal surfaces of the inhalers consists of stainless steel, anodised aluminium or is lined with an inert organic coating. One of the preferred coating consists of epoxy-phenol resin. Any kind of stainless steel may be used. Suitable epoxy-phenol resins are commercially available.

Active ingredients which may be used in the aerosol compositions to be dispensed with the inhalers of the invention are any ingredient which can be administered by inhalation and which meets problems of chemical stability in solution in HFA propellants giving rise to a decomposition when stored in conventional materials cans and in particular in aluminium cans.

In the compositions to be delivered with the MDIs of the invention the hydrofluorocarbon propellant is preferably selected from the group of HFA 134a, HFA 227 and mixtures thereof.

The co-solvent is usually an alcohol, preferably ethanol. The low volatility component, when present, is selected from the group of glycols, particularly propylene glycol, polyethylene glycol and glycerol, alkanols such as decanol (decyl alcohol), sugar alcohols including sorbitol, mannitol, lactitol and maltitol, glycofural (tetrahydro-furfurylalcohol) and dipropylene glycol, vegetable oils, organic acids for example saturated carboxylic acids including lauric acid, myristic acid and stearic acid; unsaturated carboxylic acids including sorbic acid, and especially oleic acid; saccharine, ascorbic acid, cyclamic acid, amino acids, or aspartame, esters for example ascorbyl palmitate, isopropyl myristate and tocopherol esters; alkanes for example dodecane and octadecane; terpenes for example menthol, eucalyptol, limonene; sugars for example lactose, glucose, sucrose; polysaccharides for example ethyl cellulose, dextran; antioxidants for example butylated hydroxytoluene, butylated hydroxyanisole; polymeric materials for example polyvinyl alcohol, polyvinyl acetate, polyvinyl pyrrolidone; amines for example ethanolamine, diethanolamine, triethanolamine; steroids for example cholesterol, cholesterol esters. The low-volatility component has a vapour pressure at 25° C. lower than 0.1 kPa, preferably lower than 0.05 kPa.

The aerosols compositions to be delivered with the pressurised MDIs of the invention may contain from 0.2 to 2% by weight of said low volatility component.

Propylene glycol, polyethylene glycol, isopropyl myristate and glycerol are particularly preferred low-volatility components.

The function of the low volatility component is to modulate the MMAD of the aerosol particles. Being used at very low concentrations, it does not substantially affect the chemical stability of the compositions.

Examples of active ingredients include: anticholinergics such as ipratropium bromide, oxitropium bromide, tiotropium bromide; acetal corticosteroids such as budesonide, ciclesonide, rofleponide; chetal corticosteroids such as flunisolide, triamcinolone acetonide; other corticosteroids such as fluticasone propionate, mometasone furoate; short or long acting beta-adrenergic agonists such as salbutamol, formoterol, salmeterol, TA 2005 and their combinations. The active ingredients when possible may be present in racemic mixtures or in form of a single enantiomer or epimer.

As said before, WO 94/13262 teaches that problems of chemical stability of medicaments and in particular of ipratropium bromide in aerosol solution compositions can be solved adding an acid, either an inorganic acid or an organic acid, to the HFA propellant/cosolvent system.

Examples of compositions containing ipratropium bromide in HFA 134a/ethanol systems further containing an inorganic acid such as hydrochloric, nitric, phosphoric or sulfuric acid or an organic acid such as ascorbic or citric acid are provided.

We found that in solution compositions comprising ipratropium bromide, a propellant containing a hydrofluoroalkane, a cosolvent and further comprising a low volatility component:

a) different decomposition rates occur with different acids: for example we found that ipratropium bromide (20 μg/dose) in a composition of 13% (w/w) ethanol, 1.0% (w/w) glycerol, 20 μl/can of 1N hydrochloric acid and HFA 134a to 12 ml/can rapidly decomposes and after 3 months storage at 40° C. gives 85.0% average of drug remaining;

b) ipratropium bromide with or without acids is stable in stainless steel, anodised aluminium or in some types of epoxy phenol resin lined cans;

c) surprisingly certain kinds of materials, such as glass, coatings proposed in the prior-art to overcome the physical absorption phenomenon of the active ingredient, such as perfluoroalkoxyalkanes and fluorinated-ethylene-propylene polyether sulfone resins, or certain kinds of epoxy phenol coatings turned out to be completely unsatisfactory and ineffective in preventing its chemical degradation.

Another preferred active ingredient for the preparation of solution compositions in a HFA/cosolvent system to be dispensed by MDIs according to the present invention is budesonide.

Previously HFA/budesonide compositions have been described, in which budesonide is present in suspension in the propellant system and the composition further comprises additional ingredients such as particular kinds of surfactants (EP 504112, WO 93/05765, WO 93/18746, WO 94/21229).

In WO 98/13031 it is reported that suspension formulations of budesonide have a propensity to rapidly form coarse flocs upon dispersion and redispersion which may deleteriously affect dosage reproducibility. There is also a tendency for budesonide to deposit from suspension onto the walls of the container.

To achieve stable suspensions of particulate budesonide it is employed in the prior art a composition containing a mixture of HFA propellants to match the density of the

propellant mixture to be substantially identical to the density of budesonide, up to 3% of an adjuvant such as ethanol and small amounts of surfactant.

It is stated in the document that the levels of the adjuvants are low to avoid significant solubilization of drug, leading to a problem of chemical degradation and particle size increase on storage.

In the solution compositions of the present invention budesonide is chemically and physically stable.

The aerosol compositions of the invention distributed in inhalers having the internal surfaces consisting of stainless steel, anodised aluminium or coated with an inert material and preferably with epoxy-phenol resin are stable for long periods and do not undergo chemical degradation.

Also in this case a considerable degradation of the active ingredient was noticed when glass containers were used.

Analogously flunisolide and dexbudesonide (the 22R-epimer of budesonide) solutions in HFA propellant containing ethanol and a low-volatility component are stable when stored in inhalers having the internal surfaces consisting of anodised aluminium or coated with epoxy-phenol resin. Evident degradation of flunisolide was noticed when glass containers were used.

It has been also found that the low volatility component may also act as a co-solvent, thus increasing the solubility of the drug in the formulation and increasing the physical stability and/or allowing the possibility to decrease the quantity of co-solvent required.

The following examples further illustrate the invention. In the examples and tables the different types of epoxy phenol resins are indicated with numbers in brackets corresponding to:

(1) Epoxy-phenol lacquered aluminium vials coated by Cebal
(2) Epoxy-phenol lacquered aluminium vials coated by Presspart
(3) Epoxy-phenol lacquered aluminium vials coated by Nussbaum & Guhl
(4) Epoxy-phenol lacquered aluminium vials coated by Presspart, other than (2)

EXAMPLE 1

A composition containing 4.8 mg of ipratropium bromide (20 μg/dose), 13% (w/w) ethanol, 1.0% (w/w) glycerol and HFA 134a to 12 ml/can was distributed in stainless steel, anodised aluminium, standard aluminium cans or in cans having different internal coatings and were stored at various conditions.

The results are reported in Table 1 and Table 2.

The percent drug remaining in the composition, measured by HPLC, shows that stainless steel and anodised aluminium cans as well as epoxy-phenol resins (1), (2) and (4) coated cans are effective in preventing the chemical degradation of ipratropium bromide, differently from glass cans or other tested coatings.

EXAMPLE 2

The effect of different acids on the chemical stability of the composition of Example 1 was studied.

Citric, ascorbic and hydrochloric acids were added to the formulations in the amounts reported in Table 3.

The stability of the compositions was tested after 1, 2 and 5 months storage at 40° C. in epoxy-phenol resin (4) coated cans.

EXAMPLE 3

Compositions containing 12 mg of budesonide (50 μg/dose), 13% or 15% (w/w) ethanol, 1.3% (w/w) glycerol in HFA 134a to 12 ml/can were distributed in stainless steel, anodised aluminium, standard aluminium, glass cans or in cans having different internal coatings and were stored at various conditions.

The results are reported in Table 4 and 5.

The percent drug remaining in the compositions, measured by HPLC, shows the favourable effect of stainless steel, anodised aluminium and inert coating on the chemical stability of the active ingredient in respect to standard aluminium or glass cans. The best results have been obtained with stainless steel, anodised aluminium cans and with epoxy-phenol or perfluoroalkoxyalkane coatings.

EXAMPLE 4

A composition containing 48 mg of dexbudesonide (200 μg/dose), 15% (w/w) ethanol, 1.3% (w/w) glycerol in HFA 134a to 12 ml can was distributed in epoxy-phenol lacquered aluminium cans and was stored at 40° C.

The percent drug remaining in the composition after 8 months, measured by HPLC, was 95.4% (average value referred to two tests).

The control of the epimeric distribution showed that there is no transfer from the 22R to the 22S epimer.

EXAMPLE 5

Compositions containing 7.2, 12, 16.8 mg of dexbudesonide (corresponding to 30, 50 and 70 μg/dose respectively), ethanol, 0.9 (w/w) PEG 400 or isopropyl myristate (IPM) in HFA 227 to 12 ml can was distributed in aluminium anodised cans and was stored 70 days at 50° C. The results are reported in Table 6.

The percent drug remaining in the composition measured by HPLC shows the favourable effect of anodised aluminium cans on the chemical stability of the active ingredient. The control of the epimeric distribution showed that there is no transfer from the 22R to the 22S epimer.

EXAMPLE 6

The fine particle dose (FPD: weight of particles having an aerodynamic diameter lower than 4.7 μm) of dexbudesonide solution compositions in HFA 134a or HFA 227, prepared following the examples 4 and 5, was determined.

The experiments were performed using the Andersen Cascade Impactor and the data obtained are average values from 10 shots.

The results, reported in Table 7 and 8 show that dexbudesonide formulations of the invention are characterized by a very low dose and a very high fine particle dose.

The FPD gives a direct measure of the mass of particles within the specified size range and is closely related to the efficacy of the product.

EXAMPLE 7

A composition containing 60 mg of flunisolide (250 μg/dose), 15% (w/w) ethanol, 1% (w/w) glycerol in HFA 134a to 12 ml/can was distributed in anodised aluminium, glass cans or in cans having different internal coatings and were stored for 41 days at 50° C.

The results are reported in Table 9.

The percent drug remaining in the composition, measured by HPLC, shows the favourable effect of anodised aluminium and inert coating with epoxy-phenol resins on the chemical stability of the active ingredient in respect to glass cans.

EXAMPLE 8

The solubility of ipratropium bromide and micronized budesonide in ethanol, glycerol and their mixtures has been investigated.

The tests were carried out at room temperature.

a) Solubility in Ethanol.

About 8.5 g of absolute ethanol were weighed into a flask. The active ingredient (Ipratropium Bromide or Budesonide) was added in small amounts, under magnetic stirrer, until no further dissolution occurred (i.e.: a saturated solution was obtained). The flask was stirred for about 40 minutes, and left to settle overnight prior to analysis, to let the system equilibrate. The flask was kept sealed, to avoid evaporation.

The solution obtained was then filtered and tested for the amount of active ingredient, according to the conventional analytical procedure.

b) Solubility in Ethanol/Glycerol Mixtures.

The required amounts of ethanol and glycerol were weighted into a flask, and mixed by a magnetic stirrer until a homogeneous phase was obtained.

The solubility of ipratropium bromide in ethanol is 42.48 mg/g.

The solubility data of ipratropium bromide in ethanol/glycerol mixtures are listed in Table 10.

The solubility of micronized budesonide in ethanol is 31.756 mg/g.

Solubility data of micronized budesonide in ethanol/glycerol mixtures are listed in Table 11.

The data show that both the tested active ingredients are rather soluble in ethanol, and that their solubility increases even when small percentages of glycerol are added.

The increase in solubility is maintained also in presence of HFA propellants.

TABLE 1

Percent ipratropium bromide (IPBr) recovered after storing the composition of Example 1 for 8 months at 40° C. in cans of different types

CAN TYPE	% RESIDUAL IPBr
Epoxy-phenol resin (4)	96
Perfluoroalkoxyalkane	57
Fluorinated-ethylene-propylene/ polyether sulphone (Xylan 8840®)	78
Stainless steel	96
Standard aluminium	46

TABLE 2

Percent ipratropium bromide (IPBr) recovered after storing the composition of Example 1 for 30 and 60 days at 50° C., or for 96 days at 40° C. in cans of different types (average values referred to two tests).

	% RESIDUAL IPBr (% RESIDUAL IPBr RELATIVE TO t = 0)			
CAN TYPE	t = 0	t = 30 days at 50° C.	t = 60 days at 50° C.	t = 96 days at 40° C.
Epoxy phenol resin (1)	99	89 (90)	88.5 (89.5)	93.5 (94.5)
Epoxy phenol resin (2)	97.5	90 (92)	88.5 (90.5)	89 (91)
Epoxy phenol resin (3)	98.5	56.5 (57.5)	46 (47)	52.5 (53.5)
Anodised aluminum	94	89 (95)	87 (92.5)	90.5 (96.5)
Glass type III*	—	48.5 ( )	41.5 ( )	47 ( )

*according to Eur Pharmacopoeia 3rd Ed Suppl 1999

TABLE 3

Percent ipratropium bromide (IPBr) recovered after storing the compositions of Example 1, with different acids added, in epoxy-phenol (4) coated cans (average values referred to two tests)

	% RESIDUAL IPBr (% RESIDUAL IPBr RELATIVE TO t = 0)			
Acid	t = 0	t = 1 month at 40° C.	t = 2 months at 40° C.	t = 5 months at 40° C.
Citric				
(0.6% w/w)	98	98 (100)	99 (101)	94 (96)
(0.3% w/w)	99	99 (100)	100 (101)	97 (98)
(0.07% w/w)	99	98 (99)	99 (100)	96 (97)
Ascorbic	119	113 (95)	112 (94)	110 (92)
Hydrochloric				
(4 µl-1N)	101	100 (99)	104 (102)	96 (95)
(10 µl-1N)	101	98 (97)	98 (97)	97 (96)
(20 µl-1N)	100	95 (95)	98 (98)	97 (97)
None	97	97 (100)	98 (101)	95 (98)

TABLE 4

Percent budesonide recovered after storing the composition of Example 3 (13% ethanol) for 7 months at 40° C. in cans of different types

CAN TYPE	% RESIDUAL BUDESONIDE
Epoxy-phenol resin (4)	100
Fluorinated-ethylene-propylene/ polyether sulphone (Xylan 8840®)	93.5
Stainless steel	97
Aluminium	68
Perfluoroalkoxyalkane	100

TABLE 5

Percent budesonide recovered after storing the composition of Example 3 (15% ethanol) for 33 and 73 days at 50° C. in cans of different types (average values referred to two tests)

CAN TYPE	% RESIDUAL BUDESONIDE (% RESIDUAL BUDESONIDE RELATIVE TO t = 0) t = 0	T = 33 days	t = 73 days
Epoxy phenol resin (1)	99.3	97.0 (97.7)	95.4 (96.1)
Epoxy phenol resin (2)	99.5	96.6 (97.0)	95.6 (96.1)
Epoxy phenol resin (3)	99.3	96.6 (97.2)	95.9 (96.5)
Anodised aluminium	99.9	99.2 (99.3)	97.7 (97.8)
Glass type III*	—	86.15 (—)	80.4 (—)

*according to Eur Pharmacopoeia 3rd Ed Suppl 1999

These results have been confirmed storing the same formulation up to 7 months at 30° C., 40° C., 45° C. and 50° C.

TABLE 6

Percent dexbudesonide recovered after storing the compositions of Example 5 for 70 days at 50° C. in anodised aluminium cans (average values referred to two tests).

Metered dose (μg)	Ethanol % (w/w)	Low vol. comp. 0.9% (w/w)	% Residual dexbudesonide (% residual dexbudesonide relative to t = 0) t = 0 days	t = 70 days
30	5	PEG 400	95.8	95.8 (100)
		IPM	98.1	96.8 (98.7)
50	8	PEG 400	99.0	98.0 (98.9)
		IPM	98.0	99.4 (101)
70	7	PEG 400	95.7	93.75 (98.0)
		IPM	100.4	96.3 (96.0)

IPM = Isopropyl myristate

TABLE 7

Fine particle dose (FPD) values of dexbudesonide solution formulation in HFA 134a containing:
dexbudesonide 14.4 mg/can (60 μg/shot)
ethanol 8% (w/w)
low volatility compound 0.9% (w/w)
HFA 134a to 12 ml can (valve chamber volume = 63 μl)
MMAD = 2.0 μm

Low volatility Compound	FPD (μg)	FPF (%)	Metered dose (μg)	Delivered dose (μg)
IPM	39.9	73.6	57.9	54.2
IPM	39.4	77.4	53.2	50.9

IPM = isopropyl myristate
FPF = fine particle fraction (Fine particle dose/Delivered dose × 100)
FPD = weight of particles having an aerodynamic diameter lower than 4.7 μm
Metered dose is given by the sum of delivered dose and actuator residue.
Delivered dose is the dose delivered ex actuator.

TABLE 8

Fine particle dose (FPD) values of dexbudesonide solution formulation in HFA 227 containing:
dexbudesonide 15.12 mg/can (63 μg/shot)
ethanol 7% (w/w)
low volatility compound 0.9% (w/w)
HFA 227 to 12 ml can (valve chamber volume = 63 μl)
MMAD = 2.0 μm

Low volatility Compound	FPD (μg)	FPF (%)	Metered dose (μg)	Delivered dose (μg)
IPM	45.0	75.5	63.9	59.7
PEG 400	48.5	78.9	65.5	61.5

IPM = isopropyl myristate
FPF = fine particle fraction (Fine particle dose/Delivered dose × 100)
FPD = weight of particles having an aerodynamic diameter lower than 4.7 μm
Metered dose is given by the sum of delivered dose and actuator residue
Delivered dose is the dose delivered ex actuator

TABLE 9

Percent flunisolide recovered after storing the composition of Example 7 for 41 days at 50° C. in cans of different types (average values referred to two tests).

CAN TYPE	% RESIDUAL FLUNISOLIDE (% RESIDUAL FLUNISOLIDE RELATIVE TO t = 0)) t = 0	t = 41 days	t = 93 days
Epoxy phenol resin (1)	98.4	99.2 (101)	101.4 (103)
Epoxy phenol resin (2)	101.9	99.7 (97.8)	101.9 (100)
Epoxy phenol resin (3)	101.7	99.2 (97.5)	101.2 (99.6)
Anodised aluminum	101.6	100.4 (98.8)	100.7 (99.1)
Glass type III*	—	—	97.5 ( )

*according to Eur Pharmacopoeia 3rd Ed Suppl 1999

TABLE 10

Solubility of Ipratropium Bromide in ethanol/glycerol mixtures

Ethanol (%)	Glycerol (%)	Ipratropium Bromide solubility (mg/g)
100	0	42.8
92.6	7.4	74.0
91.9	8.1	74.7
91.3	8.7	90.5
88.4	11.6	98.0
82.6	17.4	115.6
71.4	28.6	196.7
60	40	271.6
40	60	307.2
21.1	78.9	265.7
0	100	73.4

TABLE 11

Solubility of micronized Budesonide in ethanol/glycerol mixtures

Ethanol (%)	Glycerol (%)	Budesonide solubility (mg/g)
100	0	31.756
92.5	7.5	36.264
91.9	8.1	36.277
91.3	8.7	37.328
87.7	12.3	38.364
83.3	16.7	37.209
71.4	28.6	35.768
60	40	28.962
39.9	60.1	14.840
21.1	78.9	3.990
0	100	0.214

The invention claimed is:

1. A pressurized metered dose inhaler comprising a container equipped with a metering valve and containing a pressurized solution aerosol formulation comprising:

Budesonide;

a hydrofluorocarbon propellant; and

a cosolvent present in an amount that dissolves or solubilizes said Budesonide in the mixture of cosolvent and propellant.

2. The pressurized metered dose inhaler of claim 1, wherein said cosolvent is ethanol.

3. The pressurized metered dose inhaler of claim 1, wherein said ethanol is present in an amount of 13% by weight.

4. The pressurized metered dose inhaler of claim 1, wherein said hydrofluorocarbon propellant is selected from the group consisting of HFA 227 and HFA 134a.

5. A pressurized metered dose inhaler comprising a container equipped with a metering valve and containing a pressurized solution aerosol formulation comprising:

about 0.08% by weight of Budesonide;

about 85.6% by weight of a hydrofluorocarbon propellant; and

a cosolvent present in an amount that dissolves or solubilizes said Budesonide in the mixture of cosolvent and propellant.

6. The pressurized metered dose inhaler of claim 5, wherein said cosolvent is ethanol.

7. The pressurized metered dose inhaler of claim 5, wherein said ethanol is present in an amount of 13% by weight.

8. The pressurized metered dose inhaler of claim 5, wherein said hydrofluorocarbon propellant is selected from the group consisting of HFA 227 and HFA 134a.

9. A pressurized metered dose inhaler comprising a container equipped with a metering valve and containing a pressurized solution aerosol formulation comprising:

about 0.08% by weight of Budesonide;

about 85.6% by weight of HFA 134a as a propellant; and

about 13% by weight of ethanol, wherein said ethanol is present in an amount that dissolves or solubilizes said Budesonide in the mixture of cosolvent and propellant.

10. A pressurized metered dose inhaler comprising a container equipped with a metering valve and containing a pressurized solution aerosol formulation comprising:

about 0.08% by weight of Budesonide;

about 85.6% by weight of HFA 227 as a propellant; and

about 13% by weight of ethanol, wherein said ethanol is present in an amount that dissolves or solubilizes said Budesonide in the mixture of cosolvent and propellant.

11. A solution aerosol formulation adapted for use in a pressurized aerosol container, said aerosol formulation being formulated from a composition comprising:

Budesonide;

a hydrofluorocarbon propellant; and

a cosolvent present in an amount that dissolves or solubilizes said Budesonide in the mixture of cosolvent and propellant.

12. The solution aerosol formulation of claim 11, wherein said cosolvent is ethanol.

13. The solution aerosol formulation of claim 11, wherein said ethanol is present in an amount of 13% by weight.

14. The solution aerosol formulation of claim 11, wherein said hydrofluorocarbon propellant is selected from the group consisting of HFA 227 and HFA 134a.

15. A solution aerosol formulation adapted for use in a pressurized aerosol container, said aerosol formulation being formulated from a composition comprising:

about 0.08% by weight of Budesonide;

about 85.6% by weight of a hydrofluorocarbon propellant; and

a cosolvent present in an amount that dissolves or solubilizes said Budesonide in the mixture of cosolvent and propellant.

16. The solution aerosol formulation of claim 15, wherein said cosolvent is ethanol.

17. The solution aerosol formulation of claim 15, wherein said ethanol is present in an amount of 13% by weight.

18. The solution aerosol formulation of claim 15, wherein said hydrofluorocarbon propellant is selected from the group consisting of HFA 227 and HFA 134a.

19. A solution aerosol formulation adapted for use in a pressurized aerosol container, said aerosol formulation being formulated from a composition comprising:

about 0.08% by weight of Budesonide;

about 85.6% by weight of HFA 134a as a propellant; and

about 13% by weight of ethanol, wherein said ethanol is present in an amount that dissolves or solubilizes said Budesonide in the mixture of cosolvent and propellant.

20. A solution aerosol formulation adapted for use in a pressurized aerosol container, said aerosol formulation being formulated from a composition comprising:

about 0.08% by weight of Budesonide;

about 85.6% by weight of HFA 227 as a propellant; and

about 13% by weight of ethanol, wherein said ethanol is present in an amount that dissolves or solubilizes said Budesonide in the mixture of cosolvent and propellant.

21. A pressurized metered dose inhaler comprising a container equipped with a metering valve and containing a pressurized solution aerosol formulation comprising:

about 0.08% by weight of Budesonide;

about 83.6% by weight of a hydrofluorocarbon propellant; and

a cosolvent present in an amount that dissolves or solubilizes said Budesonide in the mixture of cosolvent and propellant.

22. The pressurized metered dose inhaler of claim 21, wherein said cosolvent is ethanol.

23. The pressurized metered dose inhaler of claim 21, wherein said ethanol is present in an amount of 15% by weight.

24. The pressurized metered dose inhaler of claim 21, wherein said hydrofluorocarbon propellant is selected from the group consisting of HFA 227 and HFA 134a.

25. A solution aerosol formulation adapted for use in a pressurized aerosol container, said aerosol formulation being formulated from a composition comprising:

about 0.08% by weight of Budesonide;

about 83.6% by weight of a hydrofluorocarbon propellant; and

a cosolvent present in an amount that dissolves or solubilizes said Budesonide in the mixture of cosolvent and propellant.

26. The solution aerosol formulation of claim 25, wherein said cosolvent is ethanol.

27. The solution aerosol formulation of claim 25, wherein said ethanol is present in an amount of 15% by weight.

28. The solution aerosol formulation of claim 25, wherein said hydrofluorocarbon propellant is selected from the group consisting of HFA 227 and HFA 134a.

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